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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/407,660	09/28/1999	ERIC S. LANDER	WHIFG98-16PA	3028

21005 7590 06/27/2003

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EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/407,660	LANDER ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,27-36,38,40,42,44,46-49 and 91-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25,27-36,38,40,42,44,46-49 and 91-131* is/are rejected.

7)☒ Claim(s) *130-131* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on March 29, 2002, as well as the Reply filed July 1, 2002 (in response to a Notice of Non-Responsive Amendment), have been entered.

2. Claims 1, 12, 14, 24, 28, 31, 42, 44, and 46-49 have been amended, claims 43 and 45 have been canceled, and claims 91-131 have been added. Claims 1-25, 27-36, 38, 40, 42, 44, 46-49, and 91-131 are now under consideration.

It is noted that in applicant's Request for RCE, applicant requested entry of the enclosed amendment/reply and did not check the box requesting entry of a previously unentered After Final Amendment. Accordingly, the After Final Amendment of January 30, 2002 remains unentered, and the claims that applicant proposed adding in the Amendment, claims 50-90 (which appear to claim the same subject matter as newly added claims 91-131), are unentered and therefore canceled.

Priority

3. It is noted that the claims under consideration require method steps not disclosed in provisional application no. 60/102,069. For example, the provisional application does not disclose steps of "detecting pairs of fragments from the sample chromosomal location in the reduced representation, wherein pairs of fragments from the same chromosomal location are orthologous sequences" (as required by claims 1, 14, and 48 and claims dependent therefrom), steps of isolating fragments "which occur at the same chromosomal locus, thereby producing a pair" (as required by claims 46-47), steps of "determining the nucleotide present at one or more polymorphic sites of nucleic acid fragments containing in the reduced representation" to accomplish "genotyping the nucleic acid sample" (as required by claim 28 and claims dependent therefrom), and steps of comparing and aligning employing the particular criteria set forth in independent claims 91, 104, 117, and 128-130. Accordingly, the effective filing date of the instant claims remains the filing date of the instant application, i.e., **September 28, 1999** (see *Hunt Co. v Mallinckrodt Chemical Works*, 177 F.2d 583,587, 83 USPQ 277, 281; MPEP 201.11).

Claim Objections

4. Claims 130-131 are objected to because of the following informalities: claim 130 includes two steps designated "e" and two steps designated "f". Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> *The specification shall contain a written description of the invention, and of the manner and* process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-25, 27-36, 38, 40, 42, 44, and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has amended the claims such that they include a step of obtaining a "non-PCR amplified nucleic acid-containing sample." However, the specification does not recite or otherwise disclose a "non-PCR amplified nucleic acid-containing sample." While the specification does state at page 3 that "The method described herein does not require PCR," such a disclosure that a method does not requires a particular procedure or step (specifically, PCR) is not equivalent to and does not provide basis for the particular type of sample now recited in the claims. Accordingly, basis for this particular type of sample is not provided in the specification, and therefore the recitation of a "non-PCR amplified nucleic acid-containing sample" in the claims constitutes new matter.

It is noted that in the Remarks of the Amendment filed with applicant's RCE, applicant argues that the specification at page 3 further states that "The method....does not require *a priori* knowledge of the sequence of the nucleic acid

molecule to be assessed," and states that "Since Applicants clearly intended to encompass nucleic acid samples for which there was not *a priori* knowledge of the nucleotide sequence, a sample obtained without the use of PCR (i.e., a non-PCR amplified sample) is clearly encompassed within Applicants' description of the invention." This argument has been thoroughly considered but is not persuasive. While the specification discloses many types of "nucleic acid-containing" samples (see, e.g., pages 9-10) – any of which could be added to the claims without introducing new matter - the particular type of sample now recited in the claims is not one of those disclosed. While the recitation "nucleic acid-containing sample" is clearly very broad, the use of this broad terminology does not entitle applicant to now introduce previously undisclosed species encompassed thereby. Further, while a mere rephrasing of a passage or term does not constitute new matter (as discussed in *MPEP* 2163.07), the statement in the specification that applicant's method "does not require PCR and does not require *a priori* knowledge of the sequence of the nucleic acid molecule to be assessed" does not include any disclosure of a particular type of sample or composition that might be rephrased or reworded as the term "non-PCR amplified sample." Accordingly, Applicant's arguments are not persuasive.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-13, 19-20, 28-36, 38, 40, 42, 44, and 91-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly

point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-13 and 42 are indefinite over the recitation of the limitation "the nucleic acid molecules" in step b of claim 1 because there is insufficient antecedent basis for this limitation in the claims.

Claims 6-7 are indefinite over the recitation of the limitation "the individuals" in claim 6 because there is insufficient antecedent basis for this limitation in the claims.

Claims 19-20 are indefinite over the recitation of the limitation "the individuals" in claim 19 because there is insufficient antecedent basis for this limitation in the claims.

Claims 28-36, 38, and 40 are indefinite over the recitation of the limitation "the nucleic acid molecules" in step b of claim 28 because there is insufficient antecedent basis for this limitation in the claims.

Claim 42 is indefinite over the recitation of the limitation "the two sequences" in step b of claim 42, because there is insufficient antecedent basis for this limitation in the claims.

Claim 42 is indefinite over the recitation of the limitation "within each of the first 50 bases and the last 50 bases of the sequences." It is unclear as to whether this recitation is intended to refer to the first and last 50 bases of each sequence, or to the first and last 50 bases of, e.g., the shorter of the two sequences/the aligned region of the sequences. Clarification is required.

Claim 42 is indefinite over the recitation of the limitation "wherein accepted matches are considered a pair," and because it is unclear as to how claim 42 relates back to claim 1, from which it depends. It is noted that the first step of claim 42 requires "comparing the sequences of pairs of fragments," and that step c of claim 1 (which claim 42 further limits) requires "detecting pairs of fragments." It is unclear as to how the "pairs of fragments" of claim 42 differ from or relate to the "accepted matches" that are "considered a pair;" for example, as the first step of claim 42 requires "pairs of fragments," wouldn't any of the pairs be "considered a pair" by one of skill in the art? The repeated use of the same terminology to refer to molecules that appear to require different properties is confusing and renders the claims unclear.

Claim 44 is indefinite over the recitation of the limitation "the two sequences" in step b of claim 44, because there is insufficient antecedent basis for this limitation in the claims.

Claim 44 is indefinite over the recitation of the limitation "within each of the first 50 bases and the last 50 bases of the sequences." It is unclear as to whether this recitation is intended to refer to the first and last 50 bases of each sequence, or to the first and last 50 bases of, e.g., the shorter of the two sequences/the aligned region of the sequences. Clarification is required.

Claim 44 is indefinite over the recitation of the limitation "wherein accepted matches are considered a pair," and because it is unclear as to how claim 44 relates back to claim 14, from which it depends. It is noted that the first step of

claim 44 requires "comparing the sequences of pairs of fragments," and that step c of claim 14 (which claim 44 further limits) requires "detecting pairs of fragments." It is unclear as to how the "pairs of fragments" of claim 44 differ from or relate to the "accepted matches" that are "considered a pair;" for example, as the first step of claim 44 requires "pairs of fragments," wouldn't any of the pairs be "considered a pair" by one of skill in the art? The repeated use of the same terminology to refer to molecules that appear to require different properties is confusing and renders the claims unclear.

Claims 91-103 are indefinite over the recitation of the limitation "the nucleic acid molecules" in step b of claim 91 because there is insufficient antecedent basis for this limitation in the claims.

Claims 91-131 are indefinite over the recitation of the limitation "the two sequences" in step c of independent claims 91, 104, 117, 128, 129, and 130, because there is insufficient antecedent basis for this limitation in the claims.

Claims 91-131 are indefinite over the recitation of the limitation "within each of the first 50 bases and the last 50 bases of the sequences" in step d of independent claims 91, 104, 117, 128, 129, and 130. It is unclear as to whether this recitation is intended to refer to the first and last 50 bases of each sequence, or to the first and last 50 bases of, e.g., the shorter of the two sequences/the aligned region of the sequences. Clarification is required.

Claims 91-131 are indefinite over the recitation of the limitation "wherein accepted matches are considered a pair" in step g of claims 91, 104, 117, 128, 129, and 130. It is noted that step c of claims 91, 104, 117, 128, 129, and 130

require "comparing the sequences of pairs of fragments." It is unclear as to how the "pairs of fragments" of step c differ from or relate to the "accepted matches" that are "considered a pair;" for example, as step c already requires "pairs of fragments," wouldn't any of the pairs be "considered a pair" by one of skill in the art? The repeated use of the same terminology to refer to molecules that appear to require different properties is confusing and renders the claims unclear.

Claims 91-116 and 130-131 are indefinite over the recitation of the limitation "comparing orthologous sequences..." in step h of claims 91, 104, and 130. The instant claims do not previously refer to "orthologous sequences," and it is unclear as to which of the molecules or sequences previously recited in the claims would be considered to constitute "orthologous" sequences, and further as to how step h relates back to the previously recited method steps (e.g., is step h intended to require a comparison of the "pair" of prior step g?). Clarification is required.

Claims 96-97 are indefinite over the recitation of the limitation "the individuals" in claim 96 because there is insufficient antecedent basis for this limitation in the claims.

Claim 103 is indefinite because while step h of claim 91 refers to "orthologous sequences," steps c-g of claim 91 do not. Accordingly, to the extent that the claim further limits steps c-g, there is insufficient antecedent basis for the limitation "the orthologous sequences."

Claims 109-110 are indefinite over the recitation of the limitation "the individuals" in claim 109 because there is insufficient antecedent basis for this limitation in the claims.

Claim 115 is indefinite because while step h of claim 104 refers to "orthologous sequences," steps c-e of claim 104 do not. Accordingly, to the extent that the claim further limits steps c-e, there is insufficient antecedent basis for the limitation "the orthologous sequences."

Claims 117-127 are indefinite because it is unclear as to how steps c-g relate to "genotyping the nucleic acid sample." It is noted that step h recites a step of "determining the nucleotide present at one or more polymorphic sites of nucleic acid fragments contained in the reduced representation," referring back to the "reduced representation" of step b. Accordingly, as it appears that "genotyping" merely requires the practice of step h on the "reduced representation" of step b, it is unclear as to how steps c-g contribute to the practice of the method of genotyping.

Claims 117-127 are indefinite over the recitation of the limitation "the nucleic acid molecules" in step b of claim 117 because there is insufficient antecedent basis for this limitation in the claims.

Claims 130-131 are indefinite because it is unclear as to how the second step designated as step e in claim 130 (which recites "obtaining a second nucleic acid-containing sample....") relates to the rest of the method steps of the claim. Particularly, it is noted that the second step designated as step f requires "determining the nucleotide present at one or more polymorphic sites identified in

(h), thereby genotyping a nucleic acid-containing sample from an individual." Accordingly, the second step e appears to be extraneous and unrelated to the remainder of the method steps, which result in genotyping. Clarification is required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-4, 8-10, 12-17, 21-22, 24-25, 27-29, 31-32, 42, 44, 46-49, 91-94, 98-100, 102-107, 111-112, 114-118, 120-121, and 128-131 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Gu et al (BioTechniques 24(5):836-837 [5/1998]).

Gu et al teach a method of identifying single nucleotide polymorphisms (SNPs) (see entire reference). In Gu et al's method, nucleic acid samples are amplified, amplification products are digested with multiple restriction enzymes, and fragments are separated by size on a gel, allowing visualization of heteroduplexes which are indicative of polymorphisms (p. 836). Gu et al exemplify the use of their method in the detection of SNPs in the canine *APOH* gene (p. 836-837).

It is noted that the amplification, restriction digestion, and gel separation taught by Gu et al constitute a "treating" of nucleic acids comprising fractionation

(by digestion) and isolation (by gel separation) that result in the production of a "reduced representation" of nucleic acid fragments; further, it is an inherent property of the restriction digestion step taught by Gu et al that it is "sequence-dependent." Gu et al's methods accomplish detection of pairs of fragments that "correspond to the same chromosomal location" (e.g., two different alleles of the *APOH* gene), and comparison of such pairs by visualization of heteroduplexes, as well as by sequencing. Additionally, Gu et al's methods result in both detection/determination of a collection of polymorphisms and in genotyping of nucleic acid sample.

With further respect to claims 1-25, 27-36, 38, 40, 42, 44, and 46-49, it is noted that Gu et al employ genomic nucleic acids that are subsequently amplified by PCR (see page 836); accordingly, the initial sample employed by Gu et al is "non-PCR amplified."

Regarding claims 42, 44, and 91-131, it is noted that Gu et al disclose pairs of molecules and method steps meeting the requirements of the claims. Specifically, Gu et al disclose the comparing and alignment of pairs of molecules that are determined (by nucleic acid sequencing) to differ only at a single position (see page 837). Such pairs are clearly encompassed by the criteria recited in the claims. It is also noted that the claims as written are sufficiently broad so as to encompass methods in which only a subset of the recited steps are actually performed, as the claims recite several steps that are performed only if the previous step achieves a particular result (see, e.g., steps c, d, e, f, and g of claim 91).

With respect to independent claims 28, 48, 117, 130, and claims dependent therefrom, it is further noted that Gu et al exemplify the use of their method in canine genotyping (p. 836-837). With respect to claims 3, 16, 93, and 106, Gu et al teach samples pooled from more than one individual (p. 836). With respect to claims 4, 17, 94, and 107, Gu et al exemplify analysis of DNA samples. Regarding claims 9, 21, 99, and 111, Gu et al exemplify digestion with enzymes including *Hae*III (p. 836). With respect to claims 10, 22, 29, 100, 112, and 118, Gu et al teach the use of agarose gels in separation (p. 836). With respect to claims 12, 24, 31, 102, 114, and 120, Gu et al teach selection of heteroduplexes, which constitute fragments comprising one allele hybridized to another allele (p. 836). With respect to claims 13, 25, 32, 103, 115, and 121, Gu et al teach the sequencing of orthologous sequences (p. 837). With respect to claims 27 and 116, Gu et al teach "selection" of a subset of fragments ranging in size "from 150 to 400 bp" (p. 836), and exemplify "selection" of fragments ranging from 90-480 bp (Fig. 1). With further respect to claims 48-49 and 130-131, it is noted that Gu et al exemplify subsequent detection of a polymorphism identified by their methods by PCR, followed by *Aci*I digestion and size separation (p. 837). Accordingly, Gu et al clearly anticipate each of the instant claims.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 6-7, 19-20, 36, 38, 40, 96-97, 109-110, and 125-127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al (BioTechniques 24(5):836-837 [5/1998]) in view of Landegren et al (Genome Res. 8(8):769-776 [8/1998]).

Gu et al teach a method of identifying single nucleotide polymorphisms (SNPs) (see entire reference). In Gu et al's method, nucleic acid samples are amplified, amplification products are digested with multiple restriction enzymes, and fragments are separated by size on a gel, allowing visualization of heteroduplexes which are indicative of polymorphisms (p. 836). Gu et al exemplify the use of their method in the detection of SNPs in the canine *APOH* gene (p. 836-837).

It is noted that the amplification, restriction digestion, and gel separation taught by Gu et al constitute a "treating" of nucleic acids comprising fractionation

(by digestion) and isolation (by gel separation) that result in the production of a "reduced representation" of nucleic acid fragments; further, it is a property of the restriction digestion step taught by Gu et al that it is "sequence-dependent." Gu et al's methods accomplish detection of pairs of fragments that "correspond to the same chromosomal location" (e.g., two different alleles of the *APOH* gene), and comparison of such pairs by visualization of heteroduplexes, as well as by sequencing. Additionally, Gu et al's methods result in both detection/ determination of a collection of polymorphisms and in genotyping of nucleic acid sample. Regarding claims 6-7, 19-20, 36, 38, and 40, it is noted that Gu et al employ genomic nucleic acids that are subsequently amplified by PCR (see page 836); accordingly, the initial sample employed by Gu et al is "non-PCR amplified." Regarding claims 96-97, 109-110, and 125-127, it is noted that Gu et al disclose pairs of molecules and method steps meeting the requirements of the claims. Specifically, Gu et al disclose the comparing and alignment of pairs of molecules that are determined (by nucleic acid sequencing) to differ only at a single position (see page 837). Such pairs are clearly encompassed by the criteria recited in the claims. It is also noted that the claims as written are sufficiently broad so as to encompass methods in which only a subset of the recited steps are actually performed, as the claims recite several steps that are performed only if the previous step achieves a particular result (see, e.g., steps c, d, e, f, and g of claim 91).

Gu et al do not teach detection of polymorphisms found in individuals that share traits, including individuals sharing a disorder, as required by instant claims

6-7, 19-20, 96-97, and 109-110. Further, Gu et al do not teach employing in their methods steps of single-base extension, hybridization to an array, and/or oligo ligation, as required by claims 36, 38, 40, and 125-127.

Regarding claims 6-7, 19-20, 96-97, and 109-110, it is noted that Landegren et al teach that "SNPs are expected to take the place of simple tandem repeat polymorphisms - microsatellites - as markers in disease gene mapping", that SNPs are more stably inherited than microsatellites, and that identification of SNPs may facilitate detection and understanding of mechanisms underlying disease (p. 769). Accordingly, in view of the teachings of Landegren et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified Gu et al's method so as to have employed that method in detecting polymorphisms common to individuals sharing a trait, including individuals suffering from a particular disorder. An ordinary artisan would have been motivated to have modified the method of Gu et al in this manner for the advantage of rapidly identifying novel, candidate disease-linked or disease-causing polymorphisms shared by individuals having a disorder of interest.

Furthermore, regarding claims 36, 38, 40, and 125-127, in view of the teachings of Landegren et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified Gu et al's method so as to have employed therein steps of single-base extension, hybridization to an array, and/or oligo ligation to determine the identity of SNPs. Landegren et al teach that each of these procedures are well known methods for

rapid detection and differentiation of SNP's (see entire reference). Specifically, Landegren et al disclose that minisequencing of SNPs, which comprises a step of single base extension, may be used for rapid analysis of multiple SNPs in a homogeneous format (p. 773). Similarly, Landegren et al teach that array hybridization may allow one to "analyze many SNPs in parallel" (p. 771) and, in combination with multiplex amplification, "greatly extend the number of SNPs analyzed at one time" (p. 774). Landegren et al also teach that SNP analysis by oligonucleotide ligation assay permits rapid, real-time detection of SNPs in a homogeneous format (p. 772-773). Accordingly, an ordinary artisan would have been motivated to have modified the method of Gu et al in order to have rapidly identified multiple polymorphisms in a homogeneous format, as taught by Landegren et al, for the advantages of improved efficiency and ease of detection.

14. Claims 5, 18, 95, and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Wu et al (DNA 8(2):135-142 [1989]).

The teachings of Gu et al are set forth in paragraph 12, above. Gu et al do not teach the use of RNA molecules in their methods of detecting polymorphisms. Wu et al teach that identification of SNPs in RNA samples allows one to analyze the presence of mutations in mRNA by, e.g., determining the ratio of normal:mutant gene transcripts expressed in an individual (p. 139). Wu et al teach that methods of SNP analysis may be "applied equally to DNA and RNA, making it possible to analyze the expression of polymorphic sequences" (p. 140). In view of the teachings of Wu et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was

made to have modified the method of Gu et al so as to have analyzed an RNA sample. An ordinary artisan would have been motivated to have made such a modification for the advantage of detecting and analyzing the presence of polymorphisms in expressed genes, as suggested by Wu et al.

15. Claims 11, 23, 30, 101, 113, and 119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Bonn et al (U.S. Patent No. 5, 585,236 [12/1996]).

The teachings of Gu et al are set forth in paragraph 12, above. Gu et al do not teach a step of isolating "fractionated" nucleic acids that is "performed using high pressure liquid chromatography (HPLC)", as required by the instant claims. Bonn et al teach an HPLC-based method of nucleic acid isolation/ separation (see entire reference). Bonn et al teach that their method may be used to separate fractionated nucleic acids (col 3, lines 23-27), and that their separation method is more efficient that gel electrophoresis, which they describe as "a rather laborious procedure consisting of many labor intensive steps that are inaccessible to automation" (col 2, lines 36-38; col 5, line 42-col 6, line 13). In view of the teachings of Bonn et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gu et al so as to have separated restricted/fractionated nucleic acids by the chromatographic method of Bonn et al. An ordinary artisan would have been motivated to have made such a modification for the advantage of improving the efficiency of nucleic acid isolation and facilitating adaptation of the method for automation, as suggested by Bonn et al.

16. Claims 33-35 and 122-124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Drmanac (U.S. Patent No. 6,025,136 [2/2000; effective filing date 12/1994]).

The teachings of Gu et al are set forth in paragraph 12, above. While Gu et al teach the sequencing of orthologous sequences (p. 837), Gu et al do not teach particular steps that may be taken to accomplish sequencing. Drmanac discloses that the sequencing of multiple restriction fragments of interest may be accomplished by methods in which fragments are amplified by cloning and/or PCR, and specifically teaches ligation of adaptors to restriction fragments and amplification of those fragments with primers that hybridize to adaptor sequences (Examples 7 and 8). Drmanac teaches that the use of universal primers complementary to adaptor sequences allows one to amplify a large number of target fragments of interest using a single primer pair (col 9, lines 29-33). In view of the teachings of Drmanac, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gu et al so as to have employed Drmanac's methods for sequencing. As Gu et al do not provide specific guidance with respect to how fragments of interest are to be sequenced, an ordinary artisan would have been motivated to have employed the method taught by Drmanac, rather than experimenting to identify an appropriate sequencing method, in order to have saved time and reagents, for the advantages of convenience and cost effectiveness. Further, as Drmanac specifically teaches that the use of universal primers complementary to adaptors provides for efficient amplification of multiple target molecules using a

single primer pair, an ordinary artisan would have been motivated to have modified the method of Gu et al so as to have performed adaptor ligation and amplification with universal primers for the advantage of efficiency.

Conclusion

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
June 26, 2003